Biophysical Journal Volume 105 December 2013 2437–2438

New and Notable

A Complex Partnership: KCNQ1 and KCNE1

Guiscard Seebohm*
Universitätsklinikum Muenster,
IfGH - Myocellular Electrophysiology,
Muenster, Germany

The *Shaker*-type K^+ channel, Kv7.1 (KCNQ1 or KvLQT1) complexed with its β-subunit, the type I transmembrane protein minK (KCNE1), forms the slow component of the delayed rectifier K^+ current in the hearts of many mammals (1,2). Mutations in the KCNQ1 (and much less frequently, KCNE1) are a leading cause of the often-fatal channelopathy Long-QT syndrome. Addition of KCNE1 to heterologously expressed KCNQ1 increases unitary conductance, drastically slows activation, suppresses inactivation and right-shifts voltage dependence of activation, and modulates pharmacology (1–10). The molecular bases of most of these effects, as well as the subunit stoichiometry, are still poorly understood. The study by Xu et al. (11) uses a combination of homology modeling, protein docking, and molecular-dynamics (MD) simulation to develop a comprehensive model of KCNQ1/KCNE1 interaction. The study is greatly enhanced by use of cysteine proximity assays to systematically test hypotheses derived from their models.

The authors first generated a KCNQ1 transmembrane region homology model based on the crystal structure of the Kv1.2-Kv2.1 paddle chimera (PDB:2R9R (12)) focusing on the extracellular surface of the α-subunit tetramer. To the KCNQ1 model, they docked KCNE1, whose model was based on the nuclear magnetic resonance of KCNE1 in LMPG (lyso-myristoylphosphatidylglycerol) micelles (PDB:2K21 (13)). Cysteine proximity assays that measure the distance between two engineered cysteine residues based on disulfide formation showed proximity of the extracellular amino acids of the S1 transmembrane helix to the S4 primary voltage sensor segment and the S5 portion of the extracellular pore domain.

The authors validate the homology models and generate additional structural insights with MD simulations. Their approach is to then incorporate two likely model complexes into a POPC (1-palmitoyl-2-oleoyl-glycero-3-phosphocholine) membrane and run MD simulations using the rigid simple-point-charge water model. The simulations are able to account for their, what we believe to be, novel and previously published observations. Again, they rigorously tested their predictions with cysteine proximity assays. The result is, to our knowledge, the first robust structural view of the extracellular region of the KCNQ1/KCNE1 channel complex in an open or preopen state. In agreement with previous data (1–3,8), their model suggests that the dramatic slowing of KCNQ1 activation by KCNE1 is due to direct constraint of the extracellular portion of the S4 voltage-sensor transmembrane domain. They found a significant degree of contact between KCNE1 and the outer pore turret, which suggests direct effects on the selectivity filter, and perhaps even the intercellular portions of the pore. This provides a potential mechanism for KCNE1-based alteration of ion selectivity and drug binding (3,8). Xu et al. (11) predict that there is only space for up to two KCNE1 in the outer domain. This limitation suggests that only one or two KCNE1 β-subunits will be accommodated simultaneously by tetrameric KCNQ1 channels. This is a strong and experimentally testable prediction that is certain to be the subject of further investigation.

In MD simulations of a model this large and complex, some reasonable compromises between accuracy and computing costs are necessary, and these provide some caveats to this work. Their rigid simple-point-charge water model has three interaction sites (each site gets a point charge assigned with the central O receiving the Lennard-Jones parameters), and is therefore not well suited to simulate atomic-level water-protein interactions. It was obviously applied here because of its simplicity and high computational efficiency. The MD simulations used a pure POPC membrane that does not include specific membrane-lipid interactions. This is a significant omission, because phosphatidylinositol 4,5-bisphosphate interactions have an extremely important role in KCNQ1/KCNE1 channel modulation and pore opening. Phosphatidylinositol 4,5-bisphosphate stabilizes specific channel states through stabilization of S6 (13); the absence of the lipid in the MD simulations may explain the observed collapse of the S6 inner gate. On the other hand, other MD simulations of KCNQ1/KCNE1 using different constraints also saw inner pore-gate closure (14), suggesting that the inner S6 gate structure may be unstable in the open state. Finally, the crucial intracellular domains of both KCNQ1 and KCNE1 are not accounted for in these models.

Since its discovery nearly 20 years ago, KCNE1 has generated far more than its share of fascination, confusion, and controversy. Doubtlessly, with their careful and elaborate study Xu et al. (11) have made an impressive contribution toward answering a series of longstanding questions on the myriad actions of KCNE1 on KCNQ1. This work will not only serve as a springboard for further understanding of the interactions of ion channel β-subunits with pore-forming subunits, but also serve as a template

Submitted September 12, 2013, and accepted for publication October 8, 2013.

*Correspondence: guiscard.seebohm@ukmuenster.de or guiscard.seebohm@gmx.de

Editor: Randall Rasmusson.

0006-3495/13/12/2437/2 $2.00

http://dx.doi.org/10.1016/j.bpj.2013.10.022

for how to combine computational and experimental biophysics to understand complex problems in structure-function.

The author receives financial support from Deutsche Forschungsgemeinschaft No. 1077/3-1 and Interdisziplinäres Zentrum für Klinische Forschung Muenster No. IZKF-See1/012/13.

REFERENCES

1. Barhanin, J. L. F., F. Lesage, …, G. Romey. 1996. KvLQT1 and I_{sK} (minK) proteins associate to form the I_{Ks} cardiac potassium current. *Nature.* 384:78–80.
2. Sanguinetti, M. C. C. M., M. E. Curran, …, M. T. Keating. 1996. Coassembly of KvLQT1 and minK I_{sK} proteins to form cardiac I_{Ks} potassium channel. *Nature.* 384: 80–83.
3. Bett, G. C. M. M., M. J. Morales, …, R. L. Rasmusson. 2006. Ancillary subunits and stimulation frequency determine the potency of chromanol 293B block of the KCNQ1 potassium channel. *J. Physiol.* 576:755–767.
4. Lerche, C., G. Seebohm, …, A. E. Busch. 2000. Molecular impact of MinK on the enantiospecific block of I_{Ks} by chromanols. *Br. J. Pharmacol.* 131:1503–1506.
5. Pusch, M. 1998. Increase of the single-channel conductance of KvLQT1 potassium channels induced by the association with minK. *Pflugers Arch.* 437:172–174.
6. Pusch, M. M. R., R. Magrassi, …, F. Conti. 1998. Activation and inactivation of homomeric KvLQT1 potassium channels. *Biophys. J.* 75:785–792.
7. Seebohm, G., M. C. Sanguinetti, and M. Pusch. 2003. Tight coupling of rubidium conductance and inactivation in human KCNQ1 potassium channels. *J. Physiol.* 552:369–378.
8. Seebohm, G. W. P., P. Westenskow, …, M. C. Sanguinetti. 2005. Mutation of colocalized residues of the pore helix and transmembrane segments S5 and S6 disrupt deactivation and modify inactivation of KCNQ1 K^+ channels. *J. Physiol.* 563: 359–368.
9. Sesti, F., and S. A. Goldstein. 1998. Single-channel characteristics of wild-type I_{Ks} channels and channels formed with two minK mutants that cause long QT syndrome. *J. Gen. Physiol.* 112:651–663.
10. Tristani-Firouzi, M. S. M., and M. C. Sanguinetti. 1998. Voltage-dependent inactivation of the human K^+ channel KvLQT1 is eliminated by association with minimal K^+ channel (minK) subunits. *J. Physiol.* 510:37–45.
11. Xu, Y., W. Y. Meng, …, G. N. Tseng. 2013. Building KCNQ1/KCNE1 channel models and probing their interactions by molecular dynamics simulations. *Biophys. J.* 105: 2461–2473.
12. Long, S. B. T. X., X. Tao, …, R. MacKinnon. 2007. Atomic structure of a voltage-dependent K^+ channel in a lipid membrane-like environment. *Nature.* 450:376–382.
13. Zaydman, M. A. S. J., J. R. Silva, …, J. Cui. 2013. Kv7.1 ion channels require a lipid to couple voltage sensing to pore opening. *Proc. Natl. Acad. Sci. USA.* 110:13180–13185.
14. Strutz-Seebohm, N. P. M., M. Pusch, …, G. Seebohm. 2011. Structural basis of slow activation gating in the cardiac I_{Ks} channel complex. *Cell. Physiol. Biochem.* 27:443–452.